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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,477	07/09/2003	Michael A. Zeligs	9439-015	9606

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,477	ZELIGS, MICHAEL A.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/9/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of the Information Disclosure Statement filed 7/9/03 is acknowledged.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering to a subject an amount of a dietary indole, does not reasonably provide enablement for a method of preventing cervical dysplasia and /or one or more symptoms associated with cervical dysplasia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

1) The breadth of claims: claims 8-14 are directed to a method of preventing cervical dysplasia in a subject comprising administering to the subject an amount of a dietary indole selected from DIM and LTr-1. This is a very broad claim, one that is not supported by the instant specification.

2) The nature of the invention: The invention is drawn to a method of treating cervical dysplasia in a subject having cervical dysplasia comprising administering to the subject an amount of a dietary indole selected from the group consisting of DIM and LTr-1 effective to reduce one or more symptoms associated with cervical dysplasia. The rejected claims, however, are drawn to a method of preventing cervical dysplasia in a subject in danger of developing cervical dysplasia comprising administering to the subject an amount of a dietary indole selected from the group consisting of DIM and LTr-1 effective to prevent one or more symptoms associated with cervical dysplasia.

3) The state of the prior art: The state of the art recognized the use of DIM and its precursor indole-3carbinol in treating cancers or other ailments, however, there is no evidence in the prior art that the instant composition would prevent any type of cancer. A number of publications describe methods of treating cancers or factors increasing the risk of cancer (See US 6086915, and US 5948808).

4) The amount of direction provided by the inventor: There is nothing in the specification that would indicate that the current invention prevents cervical cancer. Guidance for preparing a pharmaceutical dosage form comprising DIM and/or LTr-1 that treats cancerous cell changes and potentially improves symptoms is provided in the specification. Specifically, as set forth on example 9 of the instant specification,

applicant explains that " Dramatic resolution occurred over a period of 2 weeks. During this time, a reduction and disappearance of chronic vaginal discharge which had been present and attributed to the cervical dysplasia were also noted. Following two weeks of transdermal use of DIM, V. H. began daily use of oral processed DIM at a dose of 50 mg per day of DIM. After two months of oral therapy, follow up pelvic examination revealed a more normal appearing cervix. No side effects were noted with the use of either DIM preparation." With respect to the instant method, there is a substantial gap between treatment and prevention. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

5) Predictability of the art: The prior does not teach a method of preventing cancers. Although some methods may aid in improving symptoms, there is nothing in the prior art that indicates that prevention is possible.

6) The presence or absence of working examples: Applicant describes 9 examples in the instant specification, none of which teach a method of preventing cervical cancer. Overall, applicant fails to provide examples indicating that the instant method can prevent cervical cancer by the use of a cream, suppository or capsule. What is provided in the specification is a method of treating and/or improving cervical dysplasia. Therefore, the practitioner would turn to trial and error experimentation to make/use of the instant compositions for preventing dysplasia, without guidance from the specification or the prior art.

7) The quantity of experimentation: In the instant case, there is a substantial gap between treatment, improvement and prevention. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. In order to utilize the dosage as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. An undetermined number of experimental factors utilizing a system for preventing dysplasia of an oral, cream or suppository dosage forms comprising an DIM or LTr-1, would have to be resolved by the practitioner and/or the patient because the factors are not sufficiently discussed in the specification to provide guidance to utilize the invention as claimed.

8) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Conclusion: Applicant is advised to use the phrase "reduce the risk of" instead of "prevent" in the instant claims.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claim 1, 2, 7, 8, and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Liang Jin et al (Liang, j. et al. *cancer research* **1999,** *59, 3991-3997),* hereinafter "Lang".

Liang researched whether the antiestrogenic phytochemical indole-3-carbinol (I3C), found in cruciferous vegetables, administered at physiological doses, would prevent the cervical-vaginal cancer that is promoted in mice by high doses of estrogen. The group of mice Lang compared mice that were fed a control diet with those that were fed a diet supplemented with 2000 ppm I3C. In the group fed the control diet, at a dose of estradiol of 0.125 mg per 60-day release, 19 of 25 transgenic mice developed cervical-vaginal cancer within 6 months, and the remainder had dysplasia. Only 2 mice of 24 in the group fed the I3C supplemented diet developed cancer, and the remainder had dysplasia or hyperplasia. I3C reduced dysplasia in the nontransgenic mice. These data indicate that I3C is a useful agent for reducing the risk for cervical-vaginal cancer and, possibly, other cancers with a papillomavirus component (abstract). Lang also teaches the use of I3C and its acid condensation product diindolymethane are available as supplements (page 9).

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liang Jin et al (Liang, j. et al. *cancer research* **1999,** *59, 3991-3997),*hereinafter "Liang". In view of Firestone et al. US 6001868 "Firestone", and further in view of Kunz et al. US 5981568 "Kunz".

Liang has been discussed above. Liang is deficient in disclosing the different methods of administration of the compound, and also the microparticles recited in the instant claims.

Firestone teaches bioactive derivatives of indole-3-carbinol (I3C), including pharmaceuticals comprising a pharmaceutically acceptable excipient (abstract). The compositions may be provided in any convenient form including tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, suppositories, etc. (col. 14, lines 1-8).

It would have been obvious to one of ordinary skills in the art to advance Liang's research by adding more dosage forms to administer DIM locally as well as generally to enhance the effect of the dietary supplement to patients according to their needs. Both references did not disclose the microparticles and the starch.

Both references did not teach the DIM in a microparticle form.

Kunz teaches therapeutic inhibitor of vascular smooth muscle cells. The composition comprises diindoloalkaloids (alkaloids are compounds that contain nitrogen and DIM is considered diindolalkaloids because in contains nitrogen), see col. 12 line 35+. The composition contains starch (col. 28, lines 45+), and is in the form of microparticles (see claims 13, 14, 26-28), and administered through variety of routes including oral, parenteral, rectal, and transdermal (col. 28, lines 8+).

Accordingly, it would have been obvious to one of ordinary skills in the art at the time the invention was made to make the composition comprising DIM, which is administered for cervical dysplasia in the form of microparticles to be able to increase

the routes of administration because microparticles are easy to include in different kinds of dosage forms and are easily absorbed through different routes. The expected result would be a method of administering DIM as a suppository, topical, transdermal, or oral form to improve the symptoms and reduce the risk of cervical dysplasia.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nabila Ebrahim 8/17/06

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER